REMARKS

Claims 78-81 and 94-102 are pending in the present application. Claims 43-46, 68-77, 82, 88-92 and 103-105 have been withdrawn from consideration as directed to non-elected inventions.[1] Claims 78-81 and 93-102 have been amended. New claims 106-116 have been added. Upon entry of the present Amendment, claims 78-81, 93-102 and 106-116 will be pending.

Claims 78-81 and 93-102 have been amended. Support for the amendments to claims 78-81 and 93-102 can be found throughout the application as originally filed. The claims were also amended to correct typographical errors.

New claims 106-116 have been added. Support for new claims 106-116 can be found throughout the application as filed and, in particular, in claim 93 and pages 92-93.

No new matter has been added.

Restriction Requirement

In the pending Office Action the Office notes that Applicant elected "Group II, claims 78-81 and 93-102 in Paper No. 13, filed 10/29/02 . . ." (Office Action, page 2). Applicant notes, however, that Applicant elected Group I corresponding to claims 78-81 and 93-102.

Information Disclosure Statement

Preliminarily, Applicant wishes to thank the Examiner for initialing and returning several of the PTO 1449 Forms submitted by Applicant. Applicant notes, however, that the Examiner returned one sheet (marked "Sheet 12 of 15") without initialing or signing the form. Applicant respectfully requests that the Examiner initial and return "Sheet 12 of 15". For the Examiner's convenience, Applicant encloses a copy of "Sheet 12 of 15" received by Applicant as part of the pending Office Action.

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1 Applicant notes that claim 82, directed to a method of purifying a ribonuclease or non-degradative RNA-binding protein and assigned to Group II in the Restriction Requirement mailed October 1, 2002, was omitted from the list of claims withdrawn from consideration.

Drawings

Applicant notes the "Notice of Draftsperson's Patent Drawing Review" attached to the pending Office Action. Applicant will forward corrected drawings under separate cover.

The Present Invention

The present invention is directed to, *inter alia*, double-stranded RNA enzyme substrates comprising a duplex of a first oligonucleotide and a second oligonucleotide. In some embodiments, the first and second oligonucleotides each have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages. The central portions are base-paired with each other in the duplex and at least one of the first or second oligonucleotides has portions flanking the central portions. As set forth on pages 26-27 of the application as filed, such ["RNA-like"]:[RNA] duplexes bind to their cellular mRNA target with an affinity comparable to that of a full 2'-methoxy oligodeoxynucleotide, "but, unlike the ["DNA-like"]:[RNA] duplexes, the resultant ["RNA-like"]:[RNA] duplexes are substrates for nucleolytic degradation . . .". The complex leading to degradation of the mRNA target comprises a dsRNAse associated with the ["RNA-like"]:[RNA] duplex which, in turn, is associated with the target mRNA. There are, therefore, three discrete entities that form the complex.

Rejection Under 35 U.S.C. § 102(b)

Claims 78-81 and 94-102 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Agrawal *et al.* (WO 94/01550; hereinafter "Agrawal"). The Office alleges that Agrawal discloses "double stranded RNAs [that] comprises a targeting sequence and a self-complementary sequence" (Office Action, page 3). Applicant respectfully traverses the rejection and requests that the rejection be reconsidered and withdrawn.

Agrawal reports self-stabilized antisense oligonucleotides but fails to teach the claimed invention. Each individual oligonucleotide discussed by Agrawal has two regions: a target hybridizing region and a self-complementary region. The self-complementary region:

contains oligonucleotide sequences that are complementary to other oligonucleotide

> sequences within the oligonucleotide. These other oligonucleotide sequences may be within the target hybridizing region or within the self-complementary region, or they may span both regions. The complementary sequences form base pairs, resulting in the formation of a hairpin structure, as shown in Figure 1, or a hammer-like structure, as shown in Figure 2.

(Agrawal, page 15). Agrawal further reports that the target hybridizing region is connected to the self-complementary region by various linkers including non-nucleic acid linkers.

The Office has failed to point out any disclosure in Agrawal teaching or even suggesting, for example, "A double-stranded RNA enzyme substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides each have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases." (referring to claim 78).

The Office has also failed to indicate any disclosure in Agrawal of "at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases." Modifications reported in Agrawal for increased nuclease resistance allegedly confer resistance to hairpin and hammerlike portions of molecules against double-stranded RNases, e.g. in the self-complementary region. The Agrawal reference does not appear to teach that any of the modifications lend resistance to single-stranded nucleases. For example, Agrawal states that "[t]he stability of such ribozymes according to the invention is provided by the incorporation of a self-complementary region at or near the 5' or 3' end of the ribozyme molecule. This self-complementary region results in the formation of a hairpin or hammer-like structure, thus rendering the 5' or 3' end of the molecule double-stranded, which causes the ribozyme molecule to resist nucleolytic degradation." (Agrawal, page 17). Formation of a double-stranded region by self-complementary base pairing is not a chemical modification. Indeed, the Office has failed to identify any teaching of two duplexed oligonucleotides

in a double-stranded RNA substrate wherein at least one of the oligonucleotides is chemically modified to make it resistant to single-stranded nucleases. Furthermore, Agrawal states that "the enzymatic stability afforded by the base-paired structures involving the self complementary sequences allows the use of oligonucleotide phosphodiesters, which are otherwise rapidly degraded." (Agrawal, page 19). The use of oligonucleotide phosphodiesters is not a chemical modification to render an oligonucleotide resistant to single-stranded nucleases.

The Office further alleges that Agrawal discloses:

> intercalating moieties (which clearly increases affinity between two complementarynucelic [sic] acids) at page 17, for example at page 19 it has been disclosed both modifications for increasing nuclease resistance and for increased duplex stability.

(Office Action, page 3). Applicant respectfully asserts that the Office has misinterpreted at least the discussion of intercalators provided in Agrawal. Agrawal discloses at page 17 that a self-stabilized oligonucleotide may be hyperstabilized through the incorporation of "one or more intercalating agent molecules. These oligonucleotides are hyperstabilized because the intercalating agent stabilizes the hybrid formed between the self-complementary region and the target hybridizing region" (Agrawal, page 17). Although Agrawal discusses the formation of stable duplexes of oligonucleotides, Agrawal does not disclose that the intercalator is involved in imparting nuclease resistance to the oligonucleotide. Regardless of the foregoing, an intercalator is not a chemical modification.

The Office also alleges that "the two oligonucleotides [of Agrawal] can be a target RNA sequence and a ribozyme" (Office Action, page 3), and that this duplex anticipates the pending claims. Applicant does not agree. The duplex discussed in Agrawal is different than the double-stranded RNA enzyme substrate presently claimed.

Applicant notes that ribozymes are by definition ***catalytic*** RNAs, *i.e.*, they cleave RNA targets. The duplex disclosed in Agrawal (consisting of a ribozyme bound to a target mRNA) leads to the degradation of the target mRNA. A substrate, or, as presently claimed, a double-stranded RNA enzyme substrate, is a substance acted upon by an enzyme. The double-stranded RNA enzyme substrate does not have catalytic activity. Ribozymes, whether or not they are bound to a target

mRNA, do not anticipate the double-stranded RNA enzyme substrate presently claimed.

Agrawal fails to teach a double-stranded RNA enzyme ***substrate*** comprising two oligonucleotides, the substrate comprising a first and second oligonucleotide. Instead, Agrawal reports a duplex formed through the hybridization of a ribozyme with its mRNA target. As discussed above, target mRNA is ***not*** a part of the double-stranded RNA enzyme substrate. The target mRNA is a distinct entity, distinct from both the substrate and from the dsRNase. The Office has also failed to particularly point out any disclosure in Agrawal that the ribozyme comprises a first and a second oligonucleotide, much less that the ribozyme comprises a first and a second oligonucleotide, at least one of which is chemically modified to render it resistant to single-stranded nucleases.

Notwithstanding the foregoing, in an attempt to advance prosecution, new claims 106-116 have been added. Agrawal fails to teach or even suggest new claims 106-116 for at least the reasons set forth above. New claims 106-116 recite, for example, "A double-stranded RNA enzyme substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are separate strands, . . .", *i.e.*, a duplex comprising ***two*** unlinked oligonucleotides. Select nucleotides in the first oligonucleotide base pair with select, complementary nucleotides in the second oligonucleotide. The Agrawal reference fails to teach or even suggest a duplex comprising separate, unlinked strands.

Applicant respectfully requests the reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Objection

Claim 93 was objected to as being dependent upon a rejected base claim. The Office indicates that claim 93 "would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not teach a duplex RNA comprising SEQ ID NO:8." (Office Action, page 4).

Applicant has amended claim 78, from which claim 93 depends. Applicant respectfully

asserts that claims 78 and, therefore, 93 are free of the prior art of record.

Notwithstanding the foregoing, as suggested by the Examiner, Applicant has added new claim 106 which is written in independent form and includes all of the limitations of claim 78 as originally filed. Applicant respectfully requests an early indication of the allowability of new claim 106.

Conclusion

Applicant believes the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Date: August 1, 2003

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Attachment: Copy of PTO Form "Sheet 12 of 15"